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Total Thyroidectomy Does Not Enhance Disease Control or Survival Even in High-Risk Patients With Differentiated Thyroid Cancer

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Summary Background Data

The extent of primary thyroidectomy for differentiated thyroid cancer is controversial. There are strong proponents for total thyroidectomy based on its presumed and theoretical disease control benefits. In contrast, there are equally strong advocates of less aggressive thyroidectomy with its lower hazard of parathyroid and recurrent nerve injury. The authors have addressed whether total thyroidectomy has a survival benefit justifying its use in patients with high-risk primary cancer. The major risk factors include age and the following the pathologic determinants follicular histology, vascular invasion, and extracapsular extension.

Materials and Methods

The clinical pathologic, therapeutic, prognostic, and outcome data were reviewed in 347 patients with well-differentiated thyroid cancer. Seventy-five percent were women, 216 patients were in the younger age group (low-risk) (21–50 years), 103 were in the intermediate-risk group (51–70 years), and 28 were in the high-risk group (>70 years). Included in the high-risk pathologic category were 158 patients who had follicular histology (55), extracapsular extension (107), or vascular invasion (119). Total thyroidectomy was performed in 56 patients, near or subtotal thyroidectomy in 47 patients and lobectomy in 55 patients. The 10-year disease specific survival in the overall patient group was 82% in patients with total thyroidectomy, 78% in patients with subtotal thyroidectomy, and 89% in patients with lobectomy ($p = 0.30$). There was no significant survival difference according to extent of thyroidectomy in the intermediate or high-risk groups either by age or in patients who had high-risk pathologic feature.

Conclusions

Total thyroidectomy in high-risk patients with differentiated thyroid cancer (containing follicular histology, vascular invasion, or extracapsular extension) showed no benefit over partial thyroidectomy. This suggests that the general use of total thyroidectomy is not indicated, except in highly selected patients.

The extent of primary thyroidectomy for differentiated thyroid cancer is controversial, with strong proponents for total thyroidectomy based on presumed and theoretical disease control benefits[1–4] *versus* advocates of partial thyroidectomies with its presumed equivalent disease control but lower hazard of parathyroid and recurrent nerve injury.[5–8] Although many would question the routine use of total thyroidectomy because of the hazards of hypoparathyroidism, even in the hands of expert surgeons, there appears to be a rationale for the use of more aggressive procedures in patients with high-risk primary cancer.[2,9] We previously reported our data regarding risk factors and confirmed the prognostic impact of age as initially reported by Cady et al. and others.[5,10–15] We also found a significant age-related decrement in 10-year survival, ranging from 92% in Group 1 (ages 21–50 years) to 77% in Group 2 (ages 51–70 years); and to 48% in patients older than 70 years.[16] Among the defined histologic characteristics associated with higher risk, follicular histology, vascular invasion, and extracapsular extension were more frequently observed in the older

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Table 1. DIFFERENTIATED THYROID CANCER CLINICAL AND PATHOLOGIC VARIABLES

Factor	Group I	Group II	Group III
Age Group	21–50 yrs (%)	51–70 yrs (%)	>70 yrs (%)
No. of patients	216	103	28
Female	160 (74)*	75 (73)	18 (64)
Male	56	29	10
Histology			
papillary	123 (57)	53 (51)	14 (50)
follicular	30 (14)	29 (28)‡	9 (32)‡
pap/foll.	63 (29)	21 (21)	5 (18)
Extracapsular	53 (38)	37 (49)§	17 (74)‡
Vascular invasion	61 (38)	40 (45)‖	18 (78)‡
Positive nodes	63 (29)	28 (27)	9 (32)
Multicentric	59 (23)	29 (28)	4 (15)
Extent of thyroidectomy			
Lobectomy	57	39	8
Subtotal	64	24	7
Total	59	24	8
Unknown	36	16	5

* Percentages calculated on available data in each set.
pap = papillary; foll = follicular.
† $p < 0.05$.
§ $p < 0.01$.
‡ $p < 0.001$.
‖ $p = 0.07$.
Survival at 10 years was 92% in Group I, 77% in Group II, and 48% in Group III.
cf. Dataset from Coburn MC, Wanebo HJ. Am J Surg 1995, 170:471–475.

patients, particularly those between ages 51 and 70 and those older than 70 years of age.[16] The histologic characteristics of follicular histology, extracapsular extension, and vascular invasion had significant impact on outcome as shown in other studies.[13–15,17–21] However, multivariate analysis indicated that only extracapsular extension and vascular invasion were significant.

This study focuses on analyzing the extent of surgery in patients who are deemed high risk by virtue of age and the constellation of the histologic factors including follicular histology, vascular invasion, and extracapsular extension. We have focused on the potential of total thyroidectomy to counteract the risks imposed by each of these histologic factors when combined with the age factor to determine the patients who would benefit from this procedure. The improvement in tumor control for this group would, at least theoretically, offset the occasional risk of the procedure to cause hypoparathyroidism or recurrent nerve injury. An additional benefit for these patients who have total thyroidectomy is the facilitation of postthyroidectomy monitoring by I^{131} scan and thyroglobulin levels. Most are treated with subsequent ^{131}I ablation and undergo tumor suppressive therapy with thyroid hormones. It has been postulated that the combination of total thyroid removal and adjuvant ^{131}I completion should maximize disease control in these high-risk patients.

This study was conducted to evaluate the effect of total thyroidectomy compared with lesser procedures in patients with high-risk thyroid cancer. In particular, this study was performed to compare the outcome in those patients with follicular cancer or those showing extracapsular extension or vascular invasion who are at high risk by virtue of age.

PATIENTS AND METHODS

Patients included in this study are those with Stage I-III differentiated thyroid cancer treated at the University of Virginia from 1956 to 1990 and patients from the Brown University affiliated hospital systems from 1975 to 1992. These cases were reviewed by their separate tumor registries, and the data were entered into a computer database. The pertinent clinical, diagnostic, and therapeutic data were collected for each patient from independent inpatient and outpatient records. The patients were categorized according to risk factors of age (21–50, 51–70, and >70 years) and histology (follicular, extracapsular, and vascular invasion, and presence of nodal metastases or multicentricity). Within each group, the percentage rate of patients with recurrence after curative therapy was calculated and examined. Patients were subcategorized according to risk factors and then underwent to secondary analysis to examine the role of the extent of thyroidectomy, including total thyroidectomy *versus* lobectomy *versus* subtotal resection. Patients who had total thyroidectomy generally also had treatment with ^{131}I ablation and received thyroid hormones. Statistical analyses were performed using the Kaplan-Meier actuarial survival curves. Gerhardt and Wilcoxon analysis, log-rank analysis of outcome, and multivariate step-wide logistic regression analysis were performed using the Wilcoxon rank test to compare patients from all three categories and to determine prognostic factors.

RESULTS

Combining the data collected from tumor registries and hospital centers yielded 347 patients with differentiated

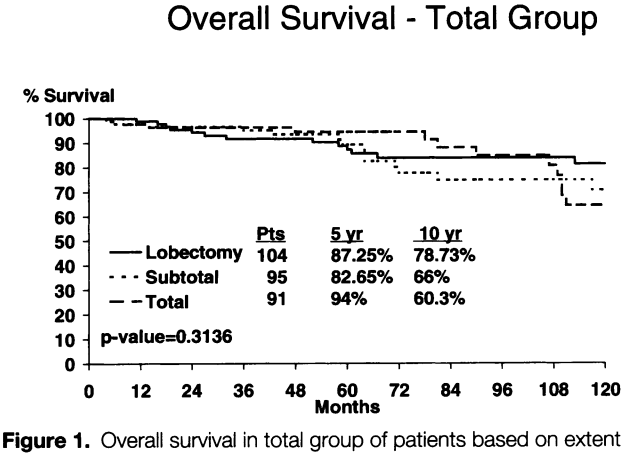

Figure 1. Overall survival in total group of patients based on extent of thyroidectomy.

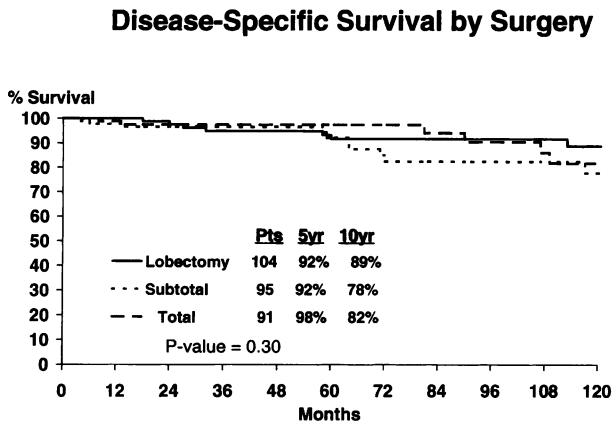

Figure 2. Disease specific survival in total group of patients based on extent of thyroidectomy.

thyroid cancer who had a mean age of 52 years (range 21–84 years); 216 tumors occurred in the 21 year to 50 year age group, 103 in the 51 year to 70 year age group, and 28 who were older than age 70. Table 1 lists the clinical pathologic variables according to age categories, and the outcome results in the three categories. As in many thyroid cancer studies, a preponderance of women dominated the registry (74%). Pure follicular histology showed an increased presence with increasing age (14% in Group 1, 28% in Group 2, and 32% in Group 3; $p < 0.001$). Other high-risk features included extracapsular extension, which was present in 38% of Group 1, 49% of Group 2 ($p = < 0.01$), and 74% in Group 3 ($p = < 0.01$). Although approximately 29% to 32% of the patients had positive nodes and multicentricity was recorded between 15% to 28%, these values were not statistically significant.

Regarding treatment, total thyroidectomy was performed in 27% of Group 1, 23% of Group 2, and 25% of Group 3. Subtotal resections were performed in 29% and 25% of Groups 1 and 2, and in 25% of Group 3. Lobectomy was performed in 29% of Group 1, 39% of Group 2, and 36% of Group 3. There were no significant differences among the groups regarding frequency of use of total thyroidectomy, lobectomy or near total thyroidectomy. Postoperative ^{131}I ablation was performed in 22% of Group 1, 24% of Group 2, and 36% of Group 3 (probability value was not significant). When Groups 2 and Group 3 were combined, 27% of patients underwent postoperative ^{131}I compared with 22% in Group 1. Overall complications were recorded in 204 of 347 patients and included 5% hypothyroidism and 5% nerve injury; only 1% had vocal cord impairment. The complication rates also were compared within the subsets of those patients who underwent total thyroidectomy *versus* those patients who were treated with partial thyroidectomy. Of the 204 patients, 65 (31%) underwent total thyroidectomy with complications of 10% hypothyroidism, 4% nerve damage, and 3% vocal cord paresis *versus* 139 (69%) patients who underwent partial thyroidectomy and had complications of 2% hypothyroidism (3 pts.), 5% nerve damage (7 pts), and 2% vocal chord impairment (3 pts.).

The effect of the extent of thyroidectomy was examined across three major age groups and according to the major risk factors (follicular histology, extracapsular extension, and vascular invasion). There was no significant impact of total thyroidectomy *versus* the lesser procedures in either the patients with the higher-risk pathologic factors or in the

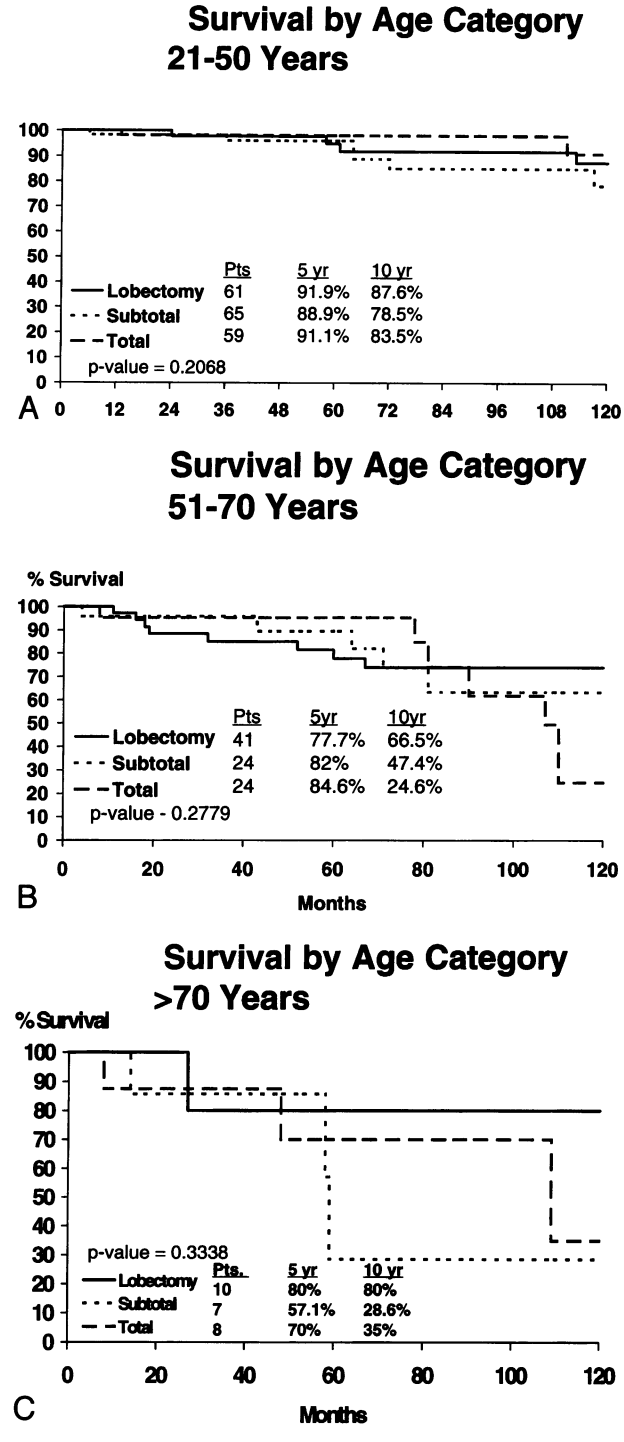

Figure 3. Survival of patients by age categories (21–50 yrs, 51–70 yrs and >70 yrs) based on extent of thyroidectomy.

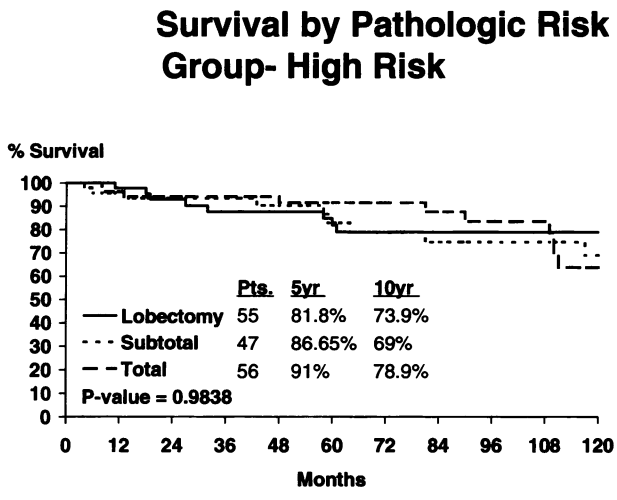

Figure 4. Survival of 158 patients with high risk pathology based on extent of thyroidectomy. With high risk pathology in the extent of thyroidectomy, in follicular (55), there were 16 total, 23 subtotal, 16 lobectomy, and 0 unknown patients; in extracapsular extension (45), there were 45 total, 29 subtotal, 33 lobectomy, and 0 unknown patients; in vascular invasion (119), there were 38 total, 29 subtotal, 28 lobectomy, and 0 unknown patients. (Some patients had more than one risk factor.)

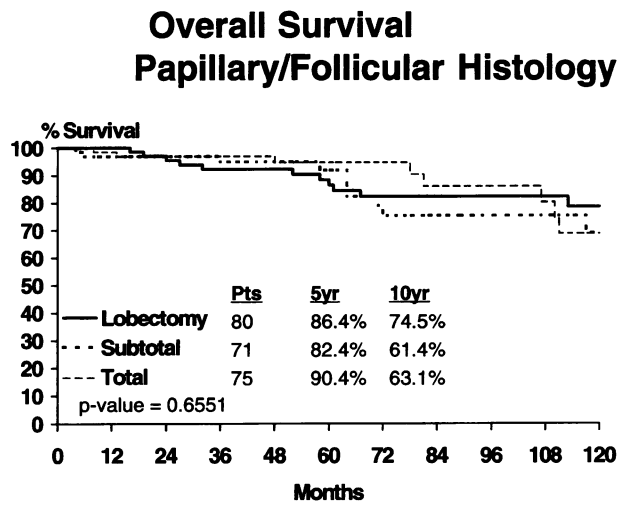

Figure 6. Overall survival of patients with papillary/follicular histology based on extent of thyroidectomy.

those with the risk related to age presented in Figs. 1–7. We also examined the effect of the extent of surgery on the pattern of recurrence in patients at high risk for disease (i.e., local/regional recurrence, distant metastases) (Table 2). Even when the high-risk patients were examined in this way, there was no significant benefit found in any of the patients in Groups 1, 2, or 3, with or without the histologic factors. Multivariate analysis also showed no prognostic impact according to type of thyroidectomy (Table 3).

COMMENTS

This study, based on an analysis of 347 adult patients, shows that the total thyroidectomy is not superior to partial thyroidectomy, subtotal resection, or to lobectomy in patients with differentiated thyroid cancer who are considered to be at high risk by virtue of age or presence of known histologic risk factors, follicular neoplasm, extracapsular extension, and vascular invasion. None of these subgroups benefited from total thyroidectomy as compared with lesser procedures. Multivariate analyses of the above risk factors, which included extent of surgery, failed to show any impact on survival based on the surgical procedure. In the analysis, only age and vascular invasion were independent prognostic factors. In the same vein, a review of complications in a subset of 204 patients for whom these were reported indicated that patients having less than total thyroidectomy had a lower rate of hypoparathyroidism, but no difference in nerve injury or vocal cord impairment.

In a previous analysis that focused on age and other prognostic factors we observed that the contribution of age to risk may be related to the increased frequency of greater

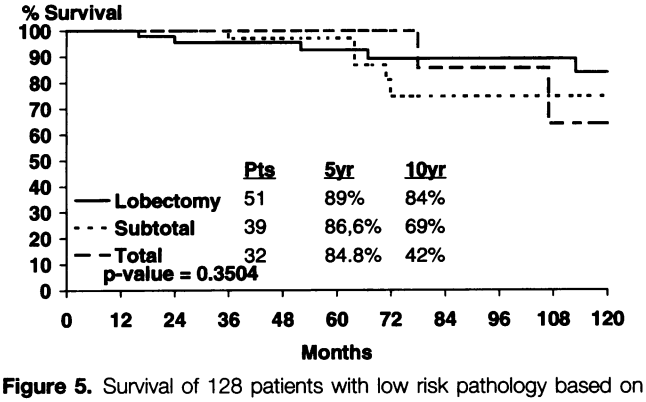

Figure 5. Survival of 128 patients with low risk pathology based on extent of thyroidectomy.

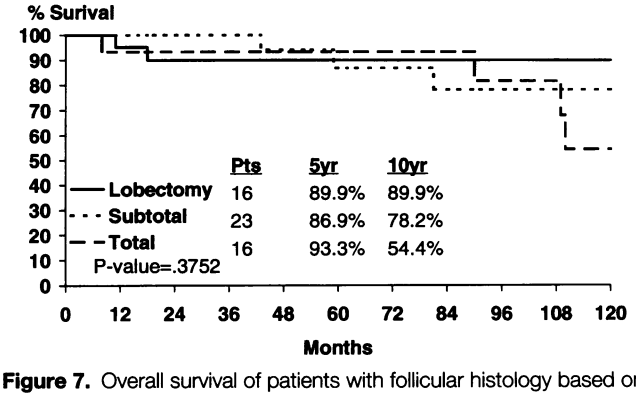

Figure 7. Overall survival of patients with follicular histology based on extent of thyroidectomy.

Table 2. EFFECT OF EXTENT OF THYROIDECTOMY ON RECURRENCE (%) AT 10 YEARS

Surgery	Pts	None (%)	Local (%)	Regional (%)	Distant (%)
Lobectomy	115	99 (86)	2 (2.6)	9 (7.8)	4 (3.5)
Subtotal	105	83 (80)	10 (9.6)	7 (6.7)	4 (3.9)
Total	103	76 (74)	9 (8.7)	17 (16.5)	1 (1.0)
Total Pts	322	258	22	33	9

Missing Data - 25 pts.
p = <0.05 (chi square); NS (Mantel-Haenszel chi square).

risk features in older patients, e.g., vascular invasion or extracapsular extension. Thus, even age, which is reported in most studies as an independent risk factor, appears to be further discriminated by the presence of known high-risk tumor factors (vascular invasion, extra capsular extension, and follicular histology), but not by the extent of surgery.

Using a multivariate analysis of a large database of papillary thyroid cancer (1779 patients with >26,000 patient year follow-up), the Mayo Clinic derived a prognostic predictive model that consists of five variables: metastasis, age, completeness of resection, invasion, and size (MACIS). A MACIS score clearly relates to outcome. The 20-year cause-specific survival ranged from 99% with a score <6, 89% for 6 to 6.99, 56% for 7 to 7.99, and 24% for MACIS score of 8+. The contribution of an incomplete operation appeared to increase with an increasing score (i.e., ranged from 0.6% of MACIS scores <6.0, to 22% for scores of 7.0 to 7.9, and 54% for scores of 8+). Although completeness of surgery was not exactly defined, it suggests that for higher-risk tumors, the ability to perform a "complete" removal of the tumor may have been limited by the extent of disease rather than a technical deficiency in performing the surgery. There may well be subgroups, however, where bilobar removal or total thyroidectomy has a clear benefit.[9] In a subset of 121 patients with higher-risk scores (>4), the above group had a higher cumulative mortality rate in 30 patients undergoing ipsilateral lobectomy (39% at 10 yrs. *versus* 28% with bilateral lobectomy, p = 0.07). Further analysis of this group eliminating those with distant metastasis indicated that the survival was better with either bilateral lobectomy or near total thyroidectomy *versus* total thyroidectomy (p = 0.002). A partial explanation of these confusing data was that the MACIS score was greater in those patients who underwent total thyroidectomy, suggesting more aggressive disease. The overall conclusion was that in either minimal or high-risk papillary cancer, total thyroidectomy did not improve outcome.

Table 3. EFFECT OF EXTENT OF THYROIDECTOMY - MULTIVARIATE ANALYSIS

	Maximum Likelihood Estimate	
	Chi Square	Risk Ratio
Total thyroidectomy	0.967	1.022
Subtotal thyroidectomy	0.2557	1.686
Follicular histology	0.59	0.755
Vascular invasion	0.032	2.597
Ext. cap. extension	0.499	1.366
Pos nodes	0.899	0.932
Age	0.0001	1.061
Size	0.876	0.981
Male	0.257	1.602

In a recent study from Memorial Sloan Kettering Hospital that focused on patterns of recurrence related to presence of extrathyroid extension, completeness of excision also had a highly significant impact (p < 0.0001), but only 31 (3%) of patients in a data base of 933 had "incomplete" excision. Multivariate analyses showed no effect of completeness of excision in patients older than 45 years (usual high-risk group) but did show a significant impact in patients younger than 45 years, which is usually a more favorable group. Completeness of excision in this series was related to gross residual tumor or positive pathologic margins, which are both clearly negative factors on outcome. Completeness of excision should be considered not equivalent to total thyroidectomy, but rather as an operation that adequately removes all disease.

The problem of pure follicular histology is not well addressed in most studies. Davis et al.[21] reviewed the scoring systems EORTC (age, grade, extent, and sizes), AGES (age, grade extent, and size), and AMES (age, metastases, extent, size) in 122 patients with pure follicular histology. AGES and EORTC significantly discriminated between high- and low-risk groups, but AMES did not do so. In multivariate analysis of low-risk groups, AGES (patient's age, perithyroidal tissue involvement, and positive frozen section) reached statistical significance. In Davis et al's. analysis, tumor size >3 cm had a borderline probability value of = 0.08 in the low-risk patients. These factors were not discriminating in the high-risk EORTC or AGES scoring system.

Mazzoferri and Jhiang reviewed 1355 patients treated in the U.S. Air Force or Ohio State University Hospitals over

a 40-year period and determined prognostic factors that related most to outcome.[22] In a Cox regression model, which excluded patients who had distant metastases, the likelihood of cancer death (and in most cases recurrence) increased by age older than 40 years, tumor size >1.5cm, local tumor invasion, regional node metastases, and delay in therapy more than 12 months. Cancer deaths were reduced in female patients having more extensive surgery than lobectomy, and in patients treated with ^{131}I. Tumor recurrence was significantly reduced in patients with Stage II and III tumors who were treated with ^{131}I *versus* those who were not treated with ^{131}I, or were treated with thyroid hormone only. The 30-year recurrence rate decreased from 38% (802 patients not treated with ^{131}I) to 10% (350 patients treated with ^{131}I). In the latter group, 61% of patients received ^{131}I for known or suspected residual disease and their cumulative recurrence rate was 20% *versus* 41% in all patients not treated with ^{131}I. In 138 patients having ^{131}I for ablation of normal gland tumor recurrence was less than 9%. Of note, the complication rate in the overall series was hypoparathyroidism in 5%, and laryngeal nerve injury in 2%. (In selected universities or large USAF referral hospitals, these rates were 2.5% and 1.05%, respectively). Accordingly, the philosophy of these authors is to recommend total or near total thyroidectomy with follow-up of ^{131}I ablation in patients at high risk for recurrence (thyroid tumor >1.5 cm, presence of local tumor recurrence, and regional nodal metastases). From their perspective, complete thyroid ablation facilitates follow-up with thyroglobulin measurements and selected ^{131}I scans to detect and ultimately treat recurrence.[23]

To put the current study into perspective, our data support that the procedure of total thyroidectomy did not significantly alter outcome in patients with high-risk differentiated thyroid cancer compared with lesser procedures of subtotal thyroidectomy or lobectomy. Although the numbers in our data base are much smaller than those in some other series, the statistical power (alpha error) is adequate enough to at least exclude the beneficial impact of extent of resection in these patients. This study suggests that in most cases, there is no benefit from the performance of total thyroidectomy and, thus, surgeons should not feel pressured to perform this procedure which still carries a defined risk for hypoparathyroidism and rare recurrent nerve injury, even in the hands of experienced surgeons. Conversely, this study does not exclude the selective use of total thyroidectomy. Patient selection for total thyroidectomy still should be based on findings at surgery and patient risk factors. These considerations include presence of large papillary tumors greater than 5 cm, presence of extrathyroid (extracapsular extension) and larger follicular tumors, (i.e., >3 cm), or patients with macroscopic nodal disease in whom a total thyroidectomy plus ^{131}I ablation may enhance local regional control in the neck and facilitate postthyroidectomy monitoring with I^{125} scan and thyroglobulin levels. Although we do not use age per se to select the extent of procedure to be performed, total thyroidectomy should be considered if local control and patient risk factors warrant such treatment in older patients (in whom the procedure was sometimes avoided because of concern for chronology rather than biology). Total thyroidectomy can be performed with a reasonably low morbidity rate by most surgeons and should be applied if tumor factors warrant. However, the true need for it appears limited.

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Discussion

DR. ROBERT M. BEAZLEY (Boston, Massachusetts): Thank you, President Wells and Secretary Copeland.

Dr. Wanebo and his co-authors have re-evaluated a large group of surgically managed thyroid cancer patients treated between 1956 and 1992, both at the University of Virginia and at the Brown University system in order to determine whether total thyroidectomy enhanced survival in high-risk patients. Their previous study determined age, follicular type, blood vessel invasion, extracapsular extension to be high-risk factors.

In this disease, identification of high-risk groups as a guide to surgical management is extremely useful, in that overall, 80% to 85% of patients have a risk of death no greater than the general population. And as Dr. Blake Cady, Hays-Martin lecturer, reported 60% of all the thyroid deaths occur in 10% of the high-risk group, and only 11% occurred in 86% of his low-risk population.

Certainly, many people would advise conservative surgery, lobectomy and isthmusectomy in low-risk patients and total or near total thyroidectomy in high-risk patients. However, I know of no prospective data to support total thyroidectomy in high-risk patients, yet many of us subscribed to it based upon the logic of it, the intuition, personal preference, or the urging of our referring endocrinologist or radiation therapist.

I must say, I guess, partly because many years ago I had a total thyroidectomy and have been very pleased with the results over the past 3 decades, I have a certain bias toward this aggressive approach.

I have tried, Dr. Wanebo, to pick your paper apart to support my position, and I really feel that I can't. I would say that I think that your two groups, your low risk and your intermediate risk groups, may be very similar. There is a very high percentage of female patients in those two groups. The average age, I think, is somewhere in the 40s, and I think there is a good deal of overlap between your low group and your intermediate group, in that the survivals are very similar, 97% and 94%.

The sticking point is in group 3, the high risk group, those patients over the age of 70, of which there were a relatively small number of patients percentage-wise in your total series, 28, and in your original paper, four of the 28 patients were not evaluable as to exactly what type of surgery they had — they were autopsy patients, I believe. There were fewer females in that group, there are more folliculars in that group, and a good deal more vascular invasion. So I guess my point is, could we be looking at a statistical bias here because of a small number in the group 3?

The other question is could there be any confounding influence of other treatments, RAI and thyroid suppression, in this group? And why did roughly half of the patients in group 3 get a lobectomy or lesser operation when it would seem to me that intuition would dictate it should be more aggressive in that group of patients with higher-risk factors.

Interesting enough, Dr. Cady's Hays-Martin lecture went on to document his work from Deaconess, where there was no difference between the treatment of his high-risk patients by lobectomy *versus* total thyroidectomy, so his group, his patients seem to confirm your findings.

My final question would be: If the wife of the chief of medicine came to you with a fairly aggressive-looking thyroid cancer, what operation are you going to do? Are you going to stick by your guns here with this data, or are you going to fall back on your old ways?

I might suggest perhaps to our president that when he gets to Chicago that perhaps the ACS oncology group could look at high-risk thyroid cancer and see if there is a role for more aggressive treatment, or should we follow the lead of Dr. Wanebo?

Thank you very much for the opportunity of the floor. [Applause]

DR. SAMUEL A. WELLS, JR. (St. Louis, Missouri): One of the trials I am sure we will do sooner or later is that. Quite frankly, there has never been, anyplace in the world, a prospective randomized trial of management of thyroid cancer. We have argued back and forth about this forever, and you can take almost any position that you wish and defend it because the data aren't there in a prospective fashion.

Maybe the correct question is what you would do to the chairman of medicine. I might treat the chairman differently than I would the chairman's wife, if they were faced with an operation.

DR. RICHARD GOLDSTEIN (Nashville, Tennessee): Dr. Wells, Dr. Copeland, Members, and Guests. In spite of the fact that patients with papillary and follicular thyroid cancer tend to have much better survival than patients with most other types of cancer, the extent of the initial surgical resection remains a fiercely debated topic.

My compliments to the authors on a well-researched report examining differentiated thyroid cancer. This study exemplifies the importance of understanding the specific tumor biology of that cancer. I do have a few comments and some questions.

Echoing one of the points that Dr. Beazley made, as this is not a randomized prospective study, can you comment on what guided the initial decision as to whether one performed a total thyroidectomy, a subtotal thyroidectomy, or a thyroid lobectomy?

Number two, an important adjunct for therapy with differentiated thyroid cancer is TSH suppression and I-131 therapy. Can you comment on patient selection for I-131 therapy and the use of TSH suppression in these patients?

Number three, as you state in your manuscript, a number of studies have identified tumor size as an independent risk factor. Yet, your analysis does not identify tumor size as an independent risk factor. Could you comment on whether you looked at tumor size as a risk factor and what you think about tumor size?

And, number four, in your comments at the end of the manuscript, you do state that consideration for total thyroidectomy should be given when one has a large papillary or a follicular cancer, the presence of extrathyroidal extension and in patients with macroscopic positive nodes. However, your data analysis suggests that total thyroidectomy offers no survival advantage.